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Sickle Cell Anemia

MEDICINE FOR THE PUBLIC

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Foreword

Americans continue to demand a greater role in deciding issues that affect their health. Increased health awareness and the convincing evidence linking lifestyle, risk factors and specific diseases have accelerated our need to know.

The Clinical Center, recognizing the importance of providing information to facilitate intelligent decisions on health issues, created a unique lecture series featuring physician scientists working at the frontiers of biomedical research at the National Institutes of Health.

The Medicine for the Public series has provided an opportunity for thousands of people to learn more about how their bodies work and what they can do to maintain or improve their health.

This publication is one of several adapted from the series. It is our sincere hope that you will find this material interesting and enlightening.

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Sickle Cell Anemia

Sickle cell anemia is a worldwide health problem, affecting many races, countries and ethnic groups. The World Health Organization estimates that each year more than 250,000 babies are born worldwide with this inherited blood cell disorder, which causes red blood cells to elongate and clog arteries. Chronic pain and life-threatening infections may result from the illness. About one in 400 black newborns in the United States have sickle cell anemia, but the disease is also prevalent in many Spanish-speaking regions of the world, such as South America, Cuba, Central America and among the Hispanic community in the United States. People in Mediterranean countries—Turkey, Greece and Italy—also have the illness. And many people, including one in 12 black Americans, carry the sickle cell trait—meaning they can pass the defect onto offspring although their own health remains excellent.

Causes

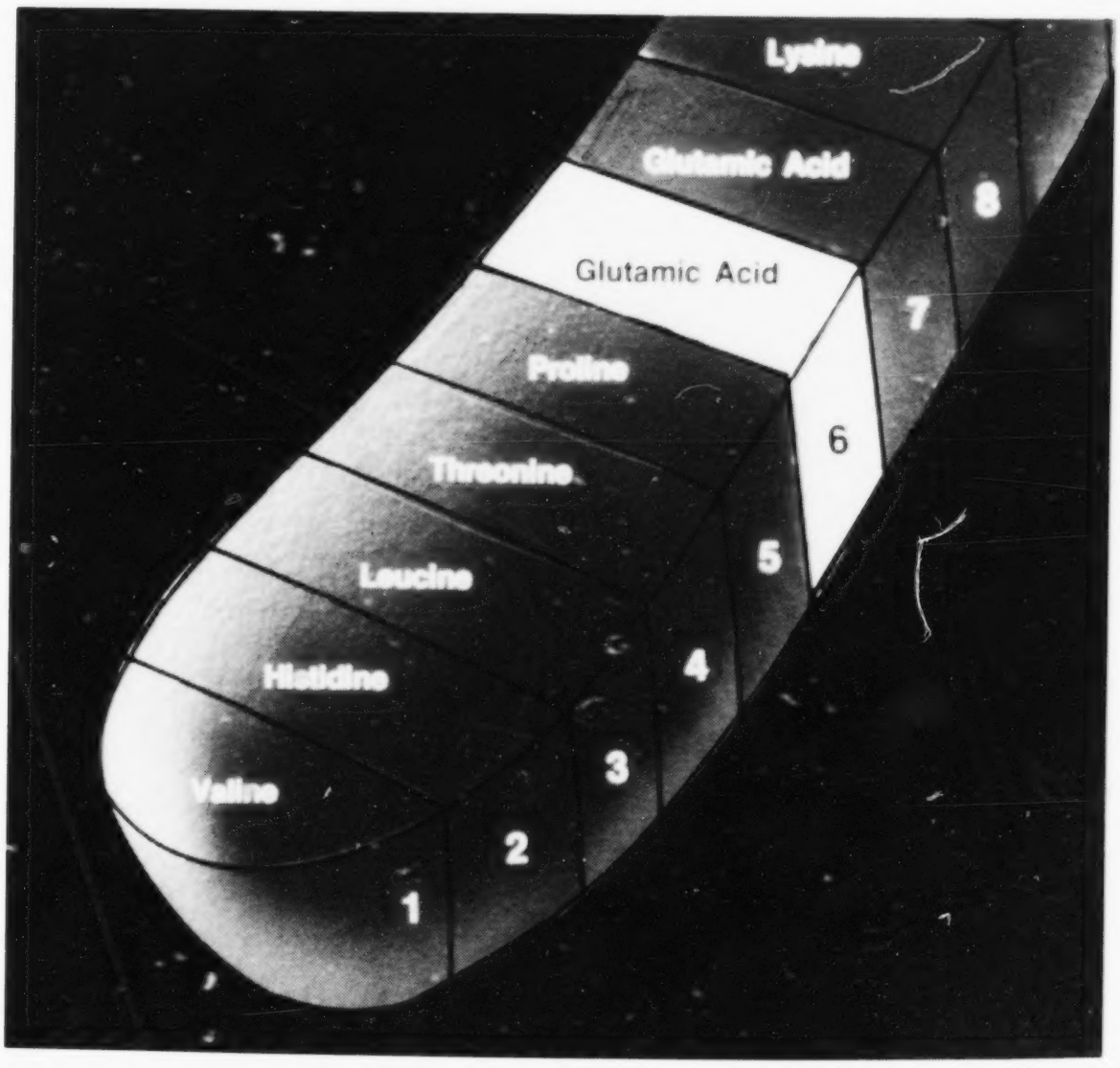
What exactly causes sickle cell anemia and how did it spread to so many different parts of the world? The answer lies in a curious coincidence. It turns out that anyone who carries the inherited trait for sickle cell anemia, but does not have the actual illness, is protected against the severe form of malaria. So in countries that had a problem with malaria, children born with sickle cell trait survived. Instead they grew up, had their own children, and passed the gene for sickle cell anemia on to these offspring. As populations migrated, the sickle cell trait and sickle cell anemia moved throughout the world.

One theory proposes that sickle cell anemia originated in Africa and, through the slave trade, spread to South America, North America and Europe. Another theory suggests the illness began in the Middle East and spread from there. Although we don't know for sure where sickle cell

anemia began, scientists have identified four separate types of genetic mutations related to the illness, each asscciated with a different geographic area—Senegal, Benin, Central Africa and the Middle East. This information excites geneticists and anthropologists because it allows them to trace the migration of populations depending on which sickle cell mutation they carry. And medically, identifying which type of mutation a person has can be critical to treatement, because the severity of disease appears to vary with the type of mutation.

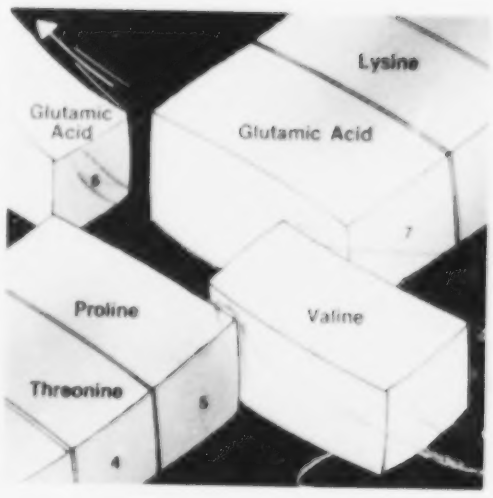
To understand the causes of sickle cell anemia, we must focus attention on a special molecule found in red blood cells. That molecule, called hemoglobin, takes oxygen from the lungs and transports it to other parts of the body. Hemoglobin's oxygen-carrying ability is essential for living, but a structural defect in the pigmented molecule can wreak havoc in the blood cell.

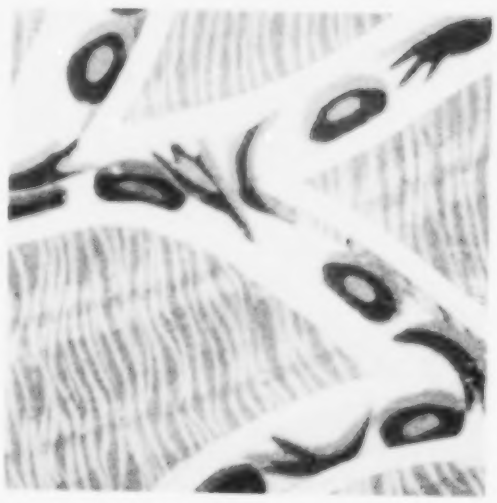
Hemoglobin contains four chains or strings of amino acids—the compounds that make up proteins. Two of the



amino acid chains are known as alpha chains, and two are called beta chains. In normal hemoglobin, the amino acid in the sixth position on the beta chains is glutamic acid. But in people with sickle cell anemia, that sixth position is occupied by another amino acid, valine, instead. This single amino acid substitution has some devastating consequences.

After releasing oxygen, hemoglobin molecules that contain the beta chain defect stick to one another instead of staying separate, forming long, rigid rods or tubules inside red blood cells. The rods cause the normally smooth, doughnut-shaped red blood cells to take on a sickle or curved shape and to lose their vital ability to deform and squeeze through tiny blood vessels. The sickled cells, which become stiff and sticky, clog small blood vessels, depriving tissue from receiving an adequate blood supply. Most of the problems associated with sickle cell anemia, including pain by ulcers, strokes and blindness, stem from this blockage.

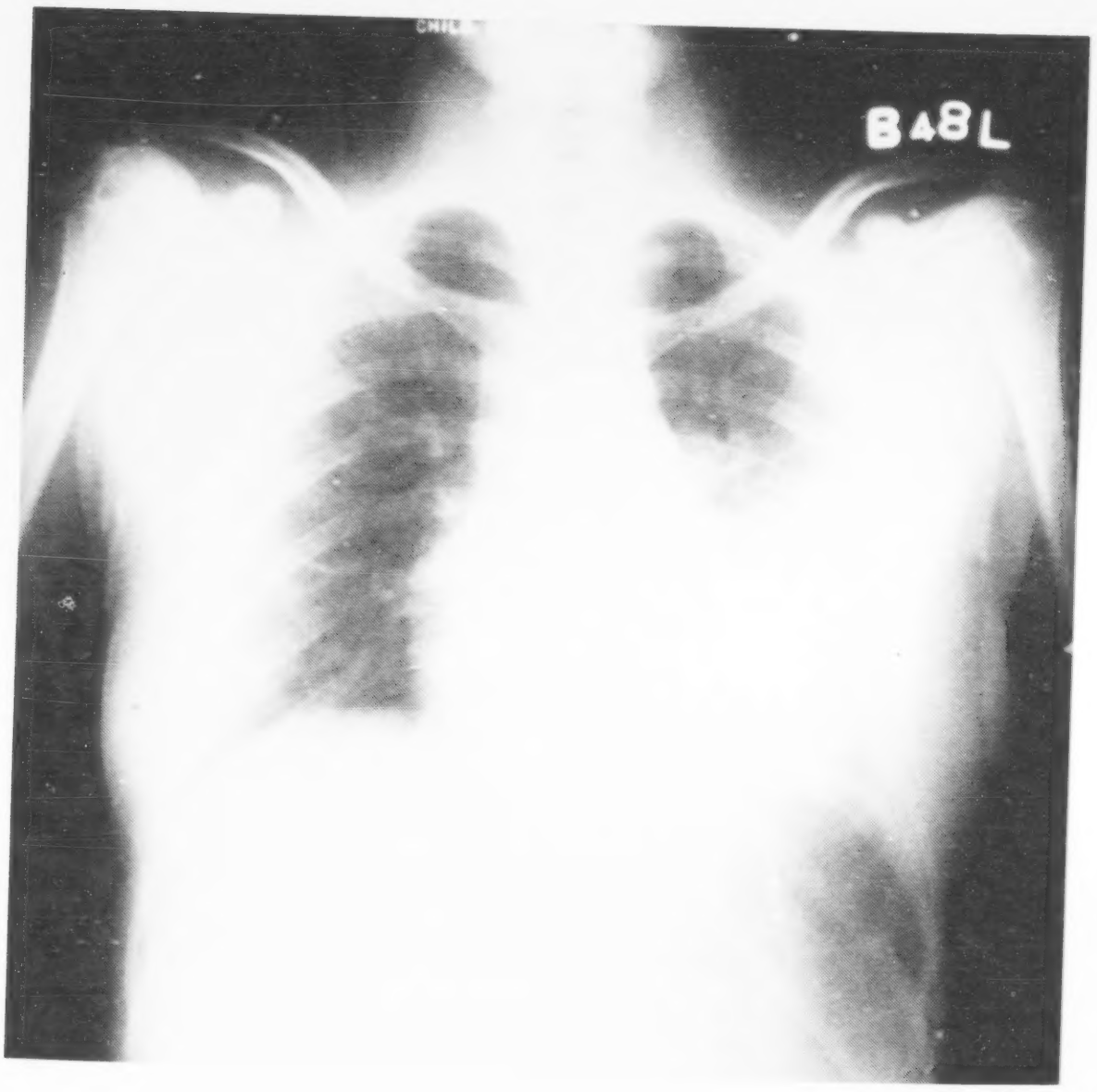




Symptoms

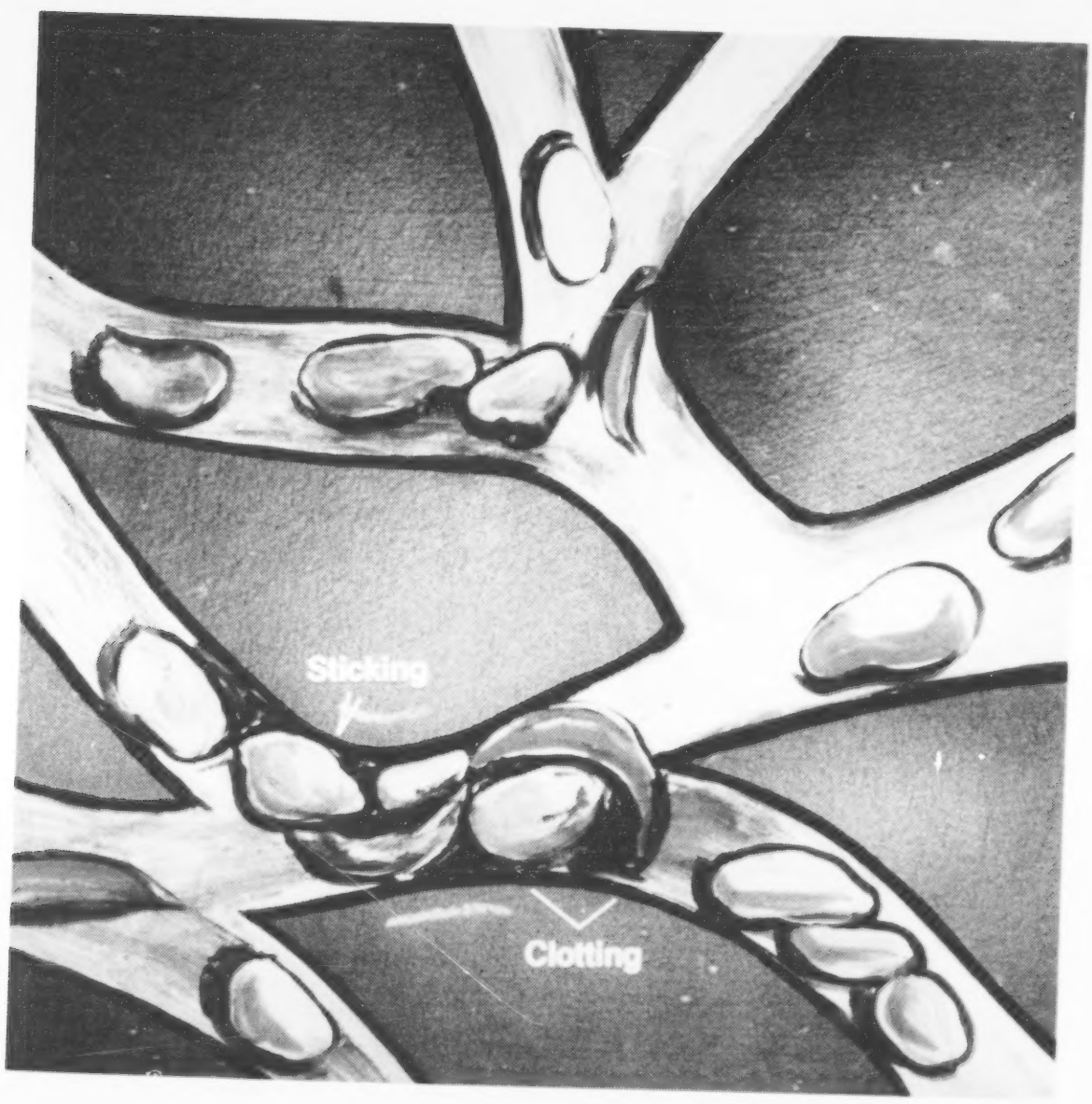
Pain caused by the blockage of sickled red blood is the most common symptom of sickle cell anemia, and it can occur unpredictably in any organ or joint of the body—wherever and whenever a blood clot develops. And as with any of the complications of the disease, the frequency and amount of pain varies widely. Some patients experience painful episodes only once a year, some may have as many as 15 to 20 episodes annually. These painful, disruptive events can be so severe that the patient may require hospitalization for five to seven days to receive intravenous fluids and narcotic pain killers. Right now, we can control the pain, but we can't stop an episode, or even identify when it may be likely to happen.

The sickle cell clots can be life-threatening, depending on where it occurs. For example, in the brain a clot may cause a stroke, leading to paralysis or death. Blood transfusions may be required every three to four weeks for an extended period to avoid recurrence of clots in the brain. Other clots may damage such vital organs as the heart, kidney, lungs, liver or eyes.



Complicating matters further, the pain associated with a clot can mimic symptoms of several other diseases, making sickle cell disease difficult to diagnose. Joint pain in sickle cell patients resembles that of arthritis, and pain in the intestines might be confused with appendicitis. A sickle-cell-induced clot in the skin can cause ulcers, a condition that may also cause the diagnosis to be missed from the underlying sickle cell problem.

As patients get older, it becomes more difficult for their heart to function normally. Lung clots may also make them more prone to pneumonia or chronic lung disease. Gall stones are common in this illness and may require surgical removal. Another particularly serious problem is the eyes. Many patients with sickle cell anemia have jaundice, causing their eyes to look yellow due to the rapid breakdown of red blood cells. But much more severe is damage to the retina, the onion-skin-thin tissue that acts as the eye's version of photographic film. Containing thousands of tiny sensors that convert light into electrical information for the brain, the retina can severely deteriorate if it is not adequately



nourished by the tiny arteries and veins which crisscross it. Blindness may result from sickle cell blockage in the retina. Because of the seriousness of the condition, opthalmologists should start examining children's eyes at the age of five.

Special Problems Among Children

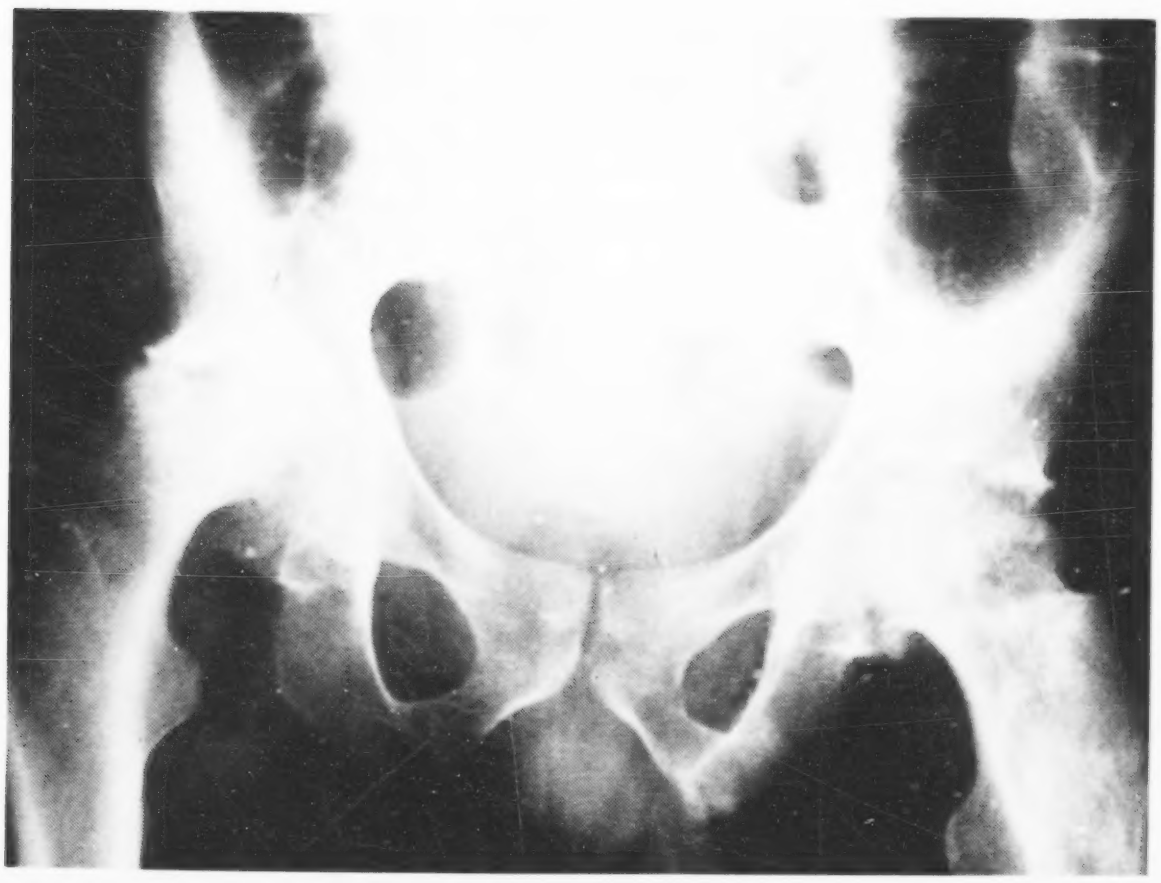
Another type of complication, which occurs more commonly in children than adults, happens when a clot forms in the hands or feet. Pain, swelling in the extremities, and fever often accompany this problem, known as hand-and-foot syndrome. A baby brought to an emergency room with fingers so swollen it appears the infant may have slammed its hand in a door may actually be suffering from sickle cell anemia. It's essential that people who take care of children know that such swelling can be a complication of the disease, one that can be verified with a simple blood test.

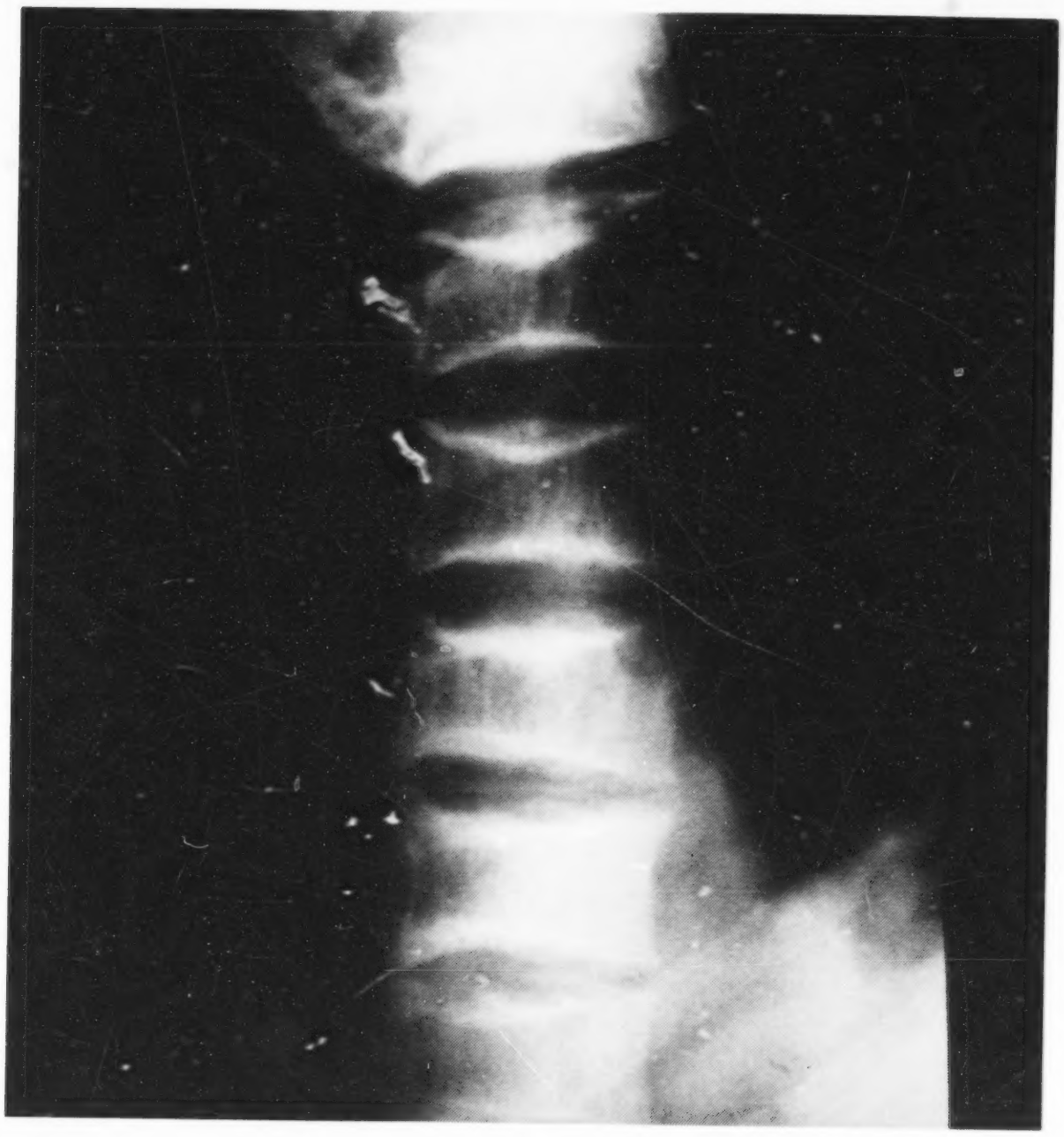
Children with sickle cell anemia may also develop severe enlargement of the spleen, so that it fills the entire abdominal cavity and blood gets trapped inside. Babies with

this condition can go into shock and die, and it is a medical emergency. Spleen enlargement can be detected and treated early, before a life-threatening condition develops. In fact, parents can be taught to feel the belly of their baby to detect spleen enlargement early on.

Because the spleen protects against infection, malfunction of this organ can also trigger severe bacterial illness. Infections in babies with sickle cell anemia are the number one killer in this disease. We now recognize that infants as young as three months can develop deadly infections, going from onset of fever to death in as little as nine hours. Moreover, a study in Los Angeles found that some babies thought to have died from Sudden Infant Death Syndrome (SIDS) actually had undiagnosed sickle cell anemia and a related infection. But new approach to management treatment can prevent many of these needless deaths and may even avoid some infections altogether. (see Treatment section)

As children with sickle cell anemia mature, they develop problems in the growth of their long bones, such as those in the spinal column or hip. Blood supply to the hip is barely adequate even in healthy people, so that patients with sickle cell diseases and its associated blockage can be especially vulnerable to hip problems. In severe cases, structural damage may require replacement with a





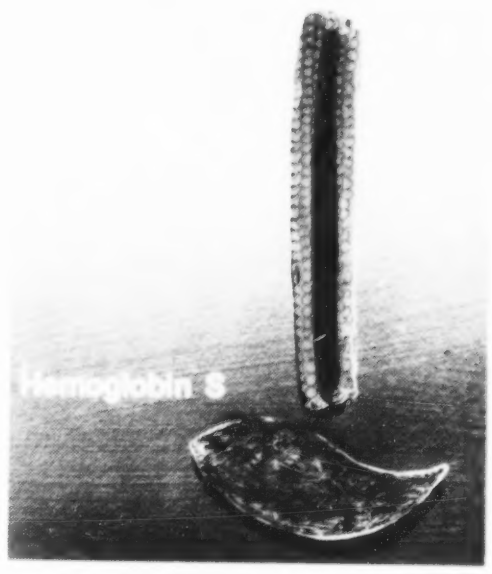
prosthesis, or artificial device. Just as serious can be damage to the spinal column, which may compress and cause severe pain.

It's important to emphasize that not all patients have every complication, and that the severity of symptoms has wide variation. Sickle cell anemia can even affect two brothers in dramatically different ways, even though they grew up in the same environment and have a similar genetic makeup.

One symptom that does affect most people is the disorder for which the disease is named—anemia, or a lack of red blood cells. Anemia occurs because sickled red blood cells last only 10 to 20 days in the bloodstream, rather than the normal 120-day life time. The sickled red blood cells are removed faster from the circulation than the bone marrow can produce them.

Genetics and Sickle Cell Anemia

There is a big distinction between someone with the sickle cell trait and someone who has the disease. To understand this bit of genetics, it's important to note that about 400 types of hemoglobin exist. Because the gene for sickling disease is recessive, a child must inherit it from both parents in order to develop the full-blown illness. Similarly, if a child inherits sickled hemoglobin from one parent, and another type of hemoglobin, called hemoglobin C, from the other parent, that child develops a variation of sickle cell disease known as SC disease. (Some other variations of sickle cell anemia exist, depending on differences in the types of hemoglobin inherited from each parent.) But if a child receives sickle hemoglobin from one parent and healthy hemoglobin from the other, that child has sickle cell trait. That child does not develop sickled cells unless subjected to extreme environmental stress. The child then goes on to live a normal life. But that person does carry the sickle trait, meaning he or she has the ability to pass the sickle gene onto offspring.



Some Misconceptions

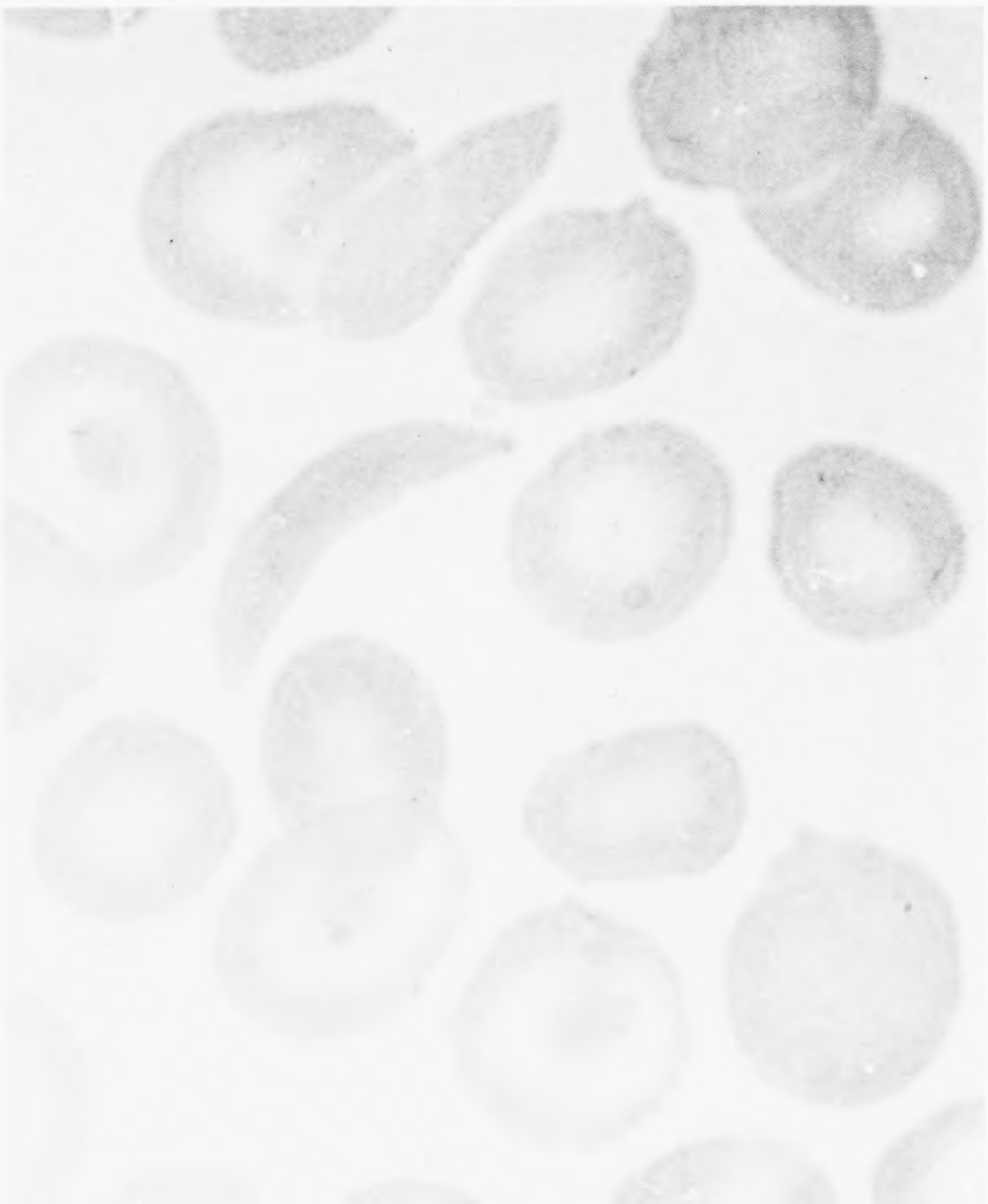
One in 12 blacks in the United States have the sickle cell trait (not the disease), and many other races and nationalities also carry the genetic defect. In the past, many people with the trait felt they should not marry or have children, for fear the children might develop the disease. In fact, there were even laws passed in this country requiring black couples to have a sickle cell test before they married. And if they did carry the trait, they were often counseled not to have children. This was never an acceptable approach. People who think they may carry the sickle trait may be tested for it if they so wish. Professionals may give counseling if asked, but the ultimate decision to have children is up to the parents, as it is for any genetic disease.

There are several other misconceptions about sickle cell anemia. One is that the illness is contagious; most people

now realize that this is not so. Another misunderstanding is that sickle cell anemia patients rarely live past the age of 20; in fact many people with the disease are in their forties, fifties and sixties.

Treatment

Sickle cell anemia currently has no cure. However, one of the most important advances in recent years has been the proof of our ability to decrease the severity of illness and the death rate in young children with this illness. As discussed earlier, infants are at great risk for overwhelming infection and death from the age of 3 months to 5 years. This infection is the main cause of death in sickle cell anemia and as many as 40 percent of the children with this type of infection have died.



However, now this does not have to occur. These are two specific approaches that we can use now to prevent this serious and life-threatening infection. First, all babies should be screened at birth to find out if they have sickle cell disease. It is a simple test and very inexpensive. It should be performed before the baby leaves the hospital and repeated in about a month to be sure of the diagnosis. If the baby has sickle cell anemia, it is very important that the baby be entered into a pediatric program, seen frequently and, most importantly, placed on penicillin by mouth every day. Studies have shown that babies given penicillin every day had their risk of infection reduced by 84 percent and no deaths occurred.

As noted earlier, one in 400 black newborns in this country has sickle cell anemia. This number highlights the urgency for early testing for the disease. In addition to the prophylactic penicillin, a team approach is needed to treat infants with the disease. Physicians, nurses and social workers, among others, can work with families to keep the baby well. Teaching parents to feel for spleen enlargement, common in children with sickle cell anemia, can also detect a serious complication early. And later, as these infants mature, we can encourage parents not to isolate them. We can also assist in providing extra instruction for children who miss school while they are treated. If we do all this, most of these children can graduate from college, and even live to see their grandchildren make a fresh start in the world.

Questions and Answers

Q. Is there any data to support the prophylactic use of penicillin in adults with sickle cell disease?

A. No, there are no data. One important reason why the treatment might not be as important in adults is that the organism *Streptococcus pneumoniae*, responsible for many infant deaths, is not as common in adults.

Q. What is the role of fetal hemoglobin in sickle cell anemia?

A. Fetal hemoglobin is produced in the womb and for six months after the baby is born. This type of hemoglobin does not seem to cause sickling as readily. And some adults with sickle cell anemia who naturally make substantial amounts of fetal hemoglobin—those from the Eastern Province of Saudi Arabia, for example—have less pain and better spleen function that other patients with this illness, including blacks in the United States. We want to figure out how we can prompt the body to manufacture more fetal hemoglobin. In fact, drugs such as hydroxyurea, which stimulate fetal hemoglobin production, are now being tested as a possible treatment for sickle cell anemia. The drugs can have serious side effects, however, and researchers are also searching for safer drugs.

Q. What should school teachers and staff know about children with sickle cell anemia and what action should they take?

A. It's essential they know as much as possible. A physician or other health care worker should alert the teacher about the child's condition. Some teachers are frightened that if the child experiences a painful episode in class, they will be unable to handle it. Education about the illness should alleviate some of this anxiety. Also, teachers who are aware a student may occasionally miss school can plan ahead, giving the child work they can do at home. In addition, some children with sickle cell anemia can be very active—playing basketball, for example—while others can not. It's important not to isolate the child who can't be active. If a child can't play a particular game, maybe he or she can coach or referee.

Q. Does sickle cell anemia protect against malaria?

A. Someone with the sickle cell trait only, and not the disease, is protected. People who have sickle cell anemia can get very, very sick from malaria.

Biography

A nationally recognized authority on sickle cell disease, Dr. Marilyn Gaston is acting chief of the sickle cell disease branch of the National Heart, Lung, and Blood Institute. As assistant professor of clinical pediatrics at Howard University and the Uniformed Services University of the Health Sciences, she also teaches medical and nursing students. She helped initiate a recent national study on young chilldren with sickle cell anemia that is expected to significantly reduce illness and death due to the disease. She also was instrumental in getting newborn screening for this illness accepted nationally.

Dr. Gaston earned her graduate degree from the University of Cincinnati College of Medicine. She completed her internship at Philadelphia General Hospital and spent her residency in pediatrics at the Cincinnati Children's Hospital Medical Center. At the University of Cincinnati, Dr. Gaston established and directed a community health center geared to low-income people. She also helped found and then directed a sickle cell treatment center at the university. These and other efforts have brought Dr. Gaston several honors, including the NIH Director's Award, the Ohio State Governor's Award, and the Public Health Service Meritorious Service Medal.